'SUPER TANK' VESSELS FOR ASEPTIC PROCESSING

by John F Swibes and Murat Altun

The idea of the 'Super Tank' vessel that would ensure much better aseptic filling in pharmaceutical production is a step nearer. The elimination of dead legs in all vessels and in all process piping will have significant positive effects with regard to increased sterility and reduced cross contamination. This article looks at the key criteria and their possible implementation resulting in better aseptic operations and cost savings over the life of the vessel.

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Introduction

In a recent paper titled 'Five Keys to Aseptic Processing Improvement & Efficiency', the author, Hal Baseman makes the case for risk-based thinking and discusses the need for innovative technologies: "I often begin conference presentations by pointing out to the audience that I started in this industry as an aseptic processing operator nearly 40 years ago. Back then, if I had been asked to predict what aseptic processing might look like 40 years in the future, I doubt I could have envisioned what it is today. And, sadly, that is because it looks pretty much the same as it did back in 1978. Our means of aseptic manufacturing, filling, contamination control, monitoring, and testing have changed little when compared with other technology-driven industries."[1]

The idea and design concepts behind the "Clean Aseptic Tank Design" (CATD) had its beginnings in the mid 1990s with a seemingly simple question: How can we clean the tank efficiently?

The perfect vessel for aseptic production would be hermetically sealed without any ports or projections. Since perfection is not achievable in a vessel intended to do work, the first compromise and therefore obstacle to cleaning is installation of various ports for connecting the necessary components. Sanitary tri-clamp (TC) ferrules and Ingold fittings were the rule at that time and the zero dead-leg (ZDL) tank flange had just been introduced.

Despite this revolutionary advancement, now more than 20 years later, most vessels designed for pharmaceutical and aseptic food processing remain largely unchanged and the zero dead-leg flange in its many iterations enjoys limited use, mostly for side-wall applications intended for sampling. These critical vessels are still designed with a multitude of standard tri-clamp ferrule and Ingold ports that can be problematic at best and in the worst

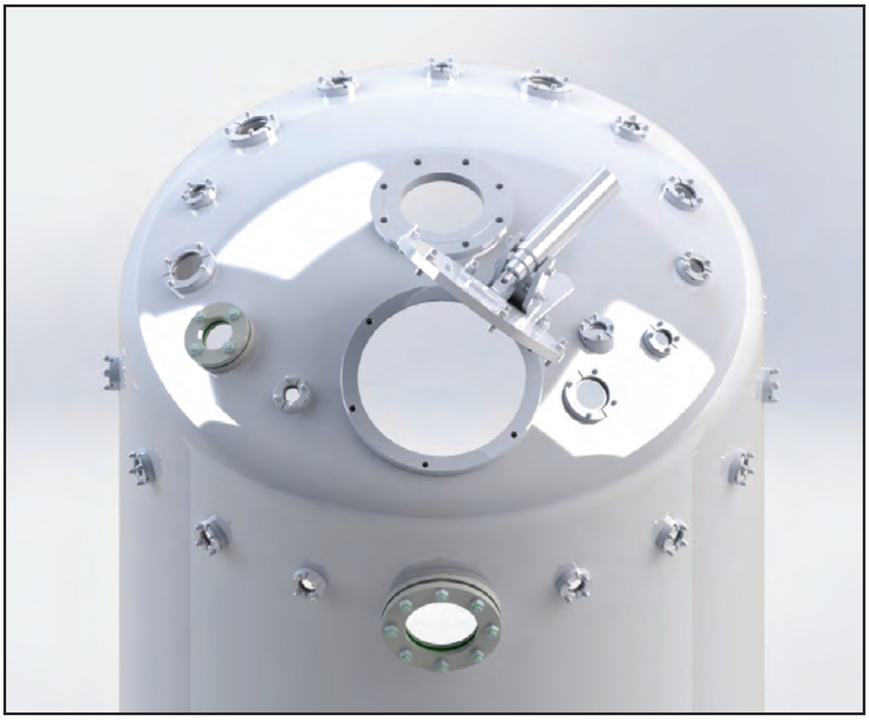

Figure 1 – Low profile zero dead leg flanges positioned both radially and vertically on vessel top eliminate potential shadow areas and significantly reduce the risk associated with insufficient cleaning with a spray device. Rendering courtesy of EMA Engineering.

case scenario, almost impossible to quickly and efficiently clean in place (CIP) and sterilize.

Today the zero dead-leg flange can be installed on the top dish of a vessel either radially or vertically as shown in **Figure 1**. The installation depends on the type of service. What is critical for our discussion is that the sealing gasket will be located as close to the inside of the vessel as possible, thereby eliminating shadow areas which inhibit ideal impingement from a spray ball.

The zero dead-leg flange concept has been advanced further with the introduction of the zero dead-leg manway. These manways are characterized by offering a very low profile to the vessel for easy cleaning with a spray ball. The other key advantage is the elimination of an air pocket that can negatively impact steam sterilization (**Figure 2**).

Preceding the introduction of the ZDL flange was the introduction of the magnetically coupled agitator and radial diaphragm bottom outlet valves. The agitators made great strides in cleanability and reducing the risk of cross contamination by eliminating hard to clean and sterilize mechanical seals. The bearing design of these systems also had another advantage: the reduction of particulates. The valves offered the advantage of a flush seal to the ID of the vessel. While the bottom mounted magnetically coupled agitator is mature technology, new developments allow for applications exceeding 50,000 liters. There are also new designs with extended shafts that allow the option for multiple impeller systems specifically engineered for bioreactors and in some cases fermenters. These new agitators can in most cases be retrofit to older or welded into new vessels. In both cases, eliminating the mechanical seals and equipment required to maintain a sterile barrier can result in valuable system improvements and reduced contamination risk, without sacrificing mixing performance.

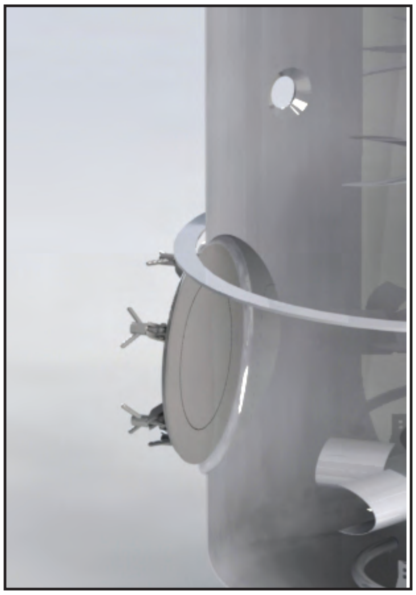

Figure 2 – Detail of tank design utilizing zero dead leg manway that exposes all surfaces to direct impingement by a spray device. Rendering courtesy of EMA Engineering with acknowledgement to Zimmerlin GmbH.

So, what is the clean aseptic tank design?

The design rules are quite simple: The vessel should be engineered with as few projections as feasible, and in every case possible, the replacement of the TC ferrule and Ingold port with a suitable zero dead-leg flange. For smaller vessels where welding multiple ports may be a problem, advances in multi-axis CNC technology allows for machining the necessary ZDL ports directly into the top head of the vessel (**Figure 3**). In special cases such as high-volume filling, multiple outlet valves can now be machined directly into the vessel bottom plate, thus ensuring equal flow to all lines and simplifying manufacturing by eliminating welding and potential warpage altogether **(Figure 4**).

In the case of agitators, top or bottom mounted magnetically coupled mixers should be considered

Figure 3 – Aseptic process vessel with zero dead leg couplings machined into the vessel top plate. No welding allows for flexibility with positioning of port locations. Image courtesy of the author.

Figure 4 – Aseptic filling vessel with multiple outlet valves machined from solid. The feed valves to the filler and the special drain contours are machined into the bottom dish which will be welded to the vessel. The configuration ensures even flow to the filler and complete draining. Image courtesy of the author.

unless the physical size of the vessel and the mixing task warrant a direct drive agitator. In these cases, proper seal design is critical. In addition to the steam block, special care should be taken with design of the mounting flange to make the agitator coupling as close to the ID of the vessel as possible.

Why it matters...

"Often in our industry, we seem to give little consideration to risk mitigation in equipment selection. Ease of assembly and operation can make a substantial difference in the risk exposure" [2]

It would be difficult to argue that TC ferrules of any size do not create hard to clean shadow areas inside vessels. The addition of standard membrane valves to many of these ports magnifies the problem and can create significant dead-legs. The importance of understanding the impact of dead-legs and the effect of the orientation of the dead-leg on the process has been explored at length by many users as well as private research organizations. One such group, The Bioprocess Institute has produced a series of videos that demonstrate the negative effects dead legs have on process piping systems, most notably the effects that low non-turbulent flow has on cleaning.

From a cleaning perspective, the TC ferrules represent a significant dead leg and shadow area. When using membrane valves, because the sealing point is at the weir located in the center of the valve, the dead leg must be calculated to this point. The shadow area created by the valve geometry near the seal makes for hard to clean areas with low turbulence and an even larger dead-leg when calculating the dead-leg by volume instead of simply linear distance. Either case is unsatisfactory for today's critical process intensification and continuous processing efforts where long run cycles are required; and any contamination will result in failure. Of course, multiple dedicated spray balls can be incorporated, but this ultimately works against the "less is more" approach.

Regardless of orientation, standard TC ferrules welded to a vessel can lag as much as 10 degrees Celsius behind the reference sensor on the side wall and even if there is only a blind cap on a ferrule. This applies also for instances where there is a diaphragm pressure gauge. If there is a vertically mounted membrane valve, the temperature difference can be even greater. In contrast, repeated steam validation studies by end-users have shown that whenever present, the zero dead-leg flange connection reaches the required temperature at the same time as the reference sensor.

The options to remedy the situation on existing vessels are few. Operators can increase the time to steam which has scheduling implications and may not solve the problem. To combat the problem, many users increase steam pressure and thus temperature which can have a direct negative impact on the performance and life of elastomeric seals as well as valve diaphragms. This is not a trivial matter since the

Figure 5 – Vessel air vent fabrication. The design adds a significant and nearly impossible to clean dead leg to the vessel top. In addition, the internal welds would be impossible to polish, contributing a significant risk to proper cleaning. Image courtesy of the internet.

generally accepted thinking is that diaphragm failures and replacements could account for as much as 50% of maintenance budgets. Even if this is a high number, the costs associated with lost product is industry wide and significant.[3] Another option available is to pull a slight vacuum on the system in order to remove the trapped gas. These systems act like an autoclave and greatly speed the introduction of steam to all parts of the system. Another benefit is using vacuum at the end of the cycle to remove all residual moisture very quickly.

A practical example is the requirement for sterile vent filters located on the top of the vessel. The typical installation uses a TC ferrule on the top of the vessel coupled with a vertically oriented membrane valve. Since membrane valves by design seal in the center of the valve, this creates a long pipe segment which is difficult to clean. However, even when membrane valves are used with a zero dead-leg flange, the inherent design limitations still introduce a significant dead-leg into the vessel. This design is not only difficult to clean in place but during steaming, represents a potential cold pocket and risks not reaching the required sterilization temperature.

Engineers have addressed these risks in various ways. The installation in **Figure 5** is one such attempt which involved a large diameter pipe fabricated with a membrane valve and an additional port for steam and or cleaning. The small welded inlet port visible at the top of the pipe may clean the top side of the valve, although it is hard to imagine that cleaning the lower half of the valve and all the lower pipe section is an easy task. A potentially overlooked detail in this installation is the welding of the small ferrule, valve body and the top cover. Welding and polishing this area would be no easy task. This results in a difficult to clean area and something that should be avoided.

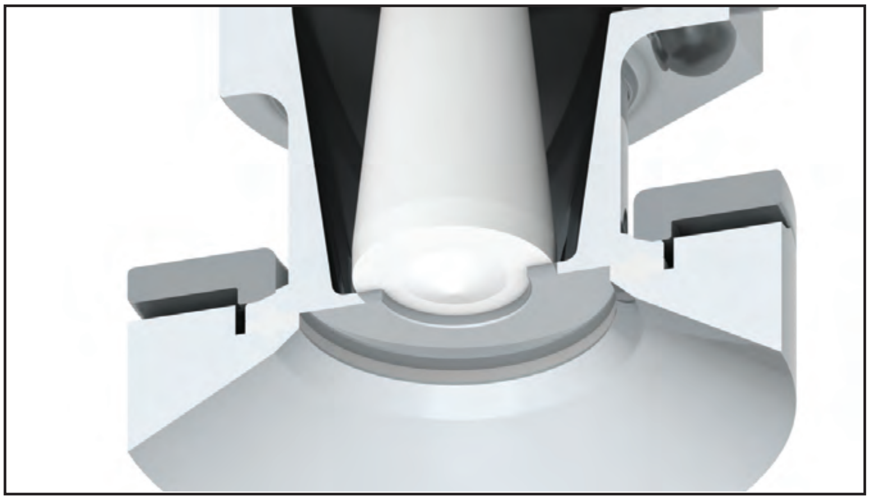

Figure 6 – Detail view of zero dead leg flange with third generation radial diaphragm valve showing the open angles accessible by a spray device which is ideal for optimal cleaning in place. Rendering courtesy of Rattiinox Srl.

A better way

The latest generation of radial diaphragm valves offer significant process design advantages simply due to the inherent geometry of the design. One critical benefit: radial diaphragm valves seal at the outside edge of the valve body. Depending on the installation location and intended service, radial valves can be produced with inlet and outlet ports at the most favorable location. This flexibility in porting results in valves that essentially eliminate dead legs. For the venting application discussed earlier there are two possible ways to proceed.

The first and arguably the most

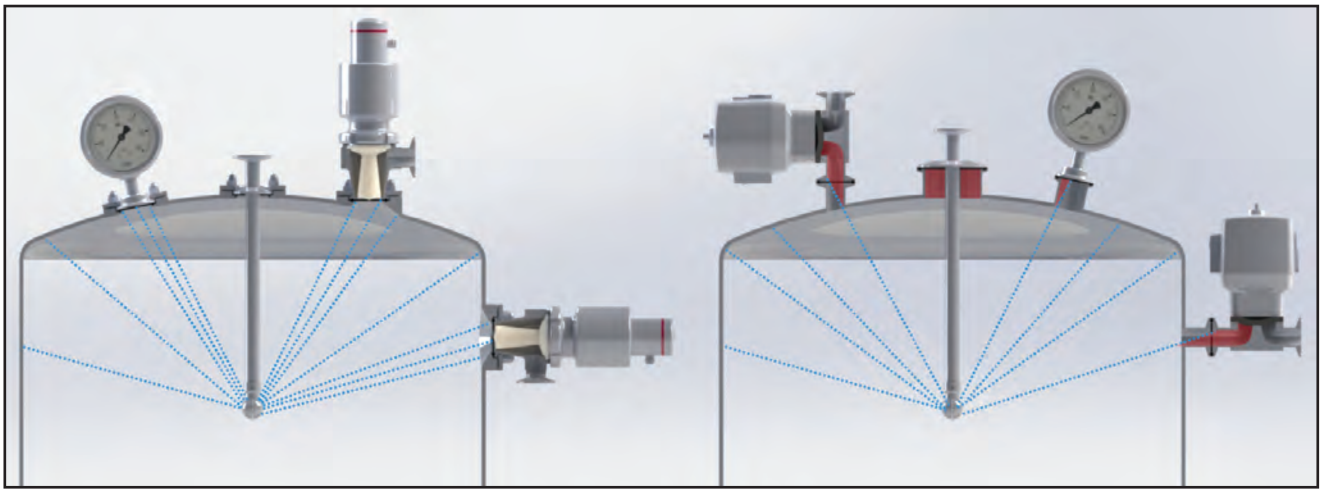

Figure 7 – Comparison of new vs old designs. Both vessels have the same capabilities and porting. However, it is clear the vessel on the left will clean faster and with more reliability. The red shaded areas in the right vessel indicate dead leg areas that cannot be cleaned properly by the spray process. Rendering courtesy of EMA Engineering.

Figure 8 – Bringing it all together: The multi-function device and well thought out valve cluster allows for multiple feed stream into the vessel utilizing the same port. By feeding various process streams in with such a device, splashing is eliminated. Reducing the required ports significantly improves the cleaning and sterilizing of the vessel. Rendering courtesy of Rattiinox Srl.

common, is to use a zero dead-leg flange and mount a valve to the port. This results in the valve seal face as close to the inner wall as possible. The area of the weld flange is completely open and reachable, without shadow areas, by a spray ball (**Figure 6**). Today's zero dead-leg flanges are widely available and ultimately very simple in concept. The device incorporates a standard TC gasket groove which is machined into a pad flange which is then welded into a vessel per the appropriate pressure vessel regulations. Valves and instruments are then fixed in place using several techniques, the most common being a split flange fixed with four nuts.

The second option is to weld the valve directly to the vessel dish in a similar way that bottom outlet valves are installed. The valve can be installed off center, and using an extended flange, the valve can be installed vertically. The outlet of the valve can point upward for the installation of a single vent filter or in the case of larger fermenters, be connected by piping to a larger exhaust filter located near the vessel. In either case the valve can be manufactured with a second port for steam or cleaning if required. In both these examples the valve sits upright conserving valuable space on the top dish. For existing vessels where there are unused TC ferrules there are now special devices that take up the dead leg in these ports like the Ingold blind plug. These simply devices can have a significant and positive impact on cleaning and sterilization efficiency by presenting a flush connection to the inside of the vessel (**Figure 7**).

The Dip Tube – space saving multi function device

Another key consideration and challenge for the Aseptic Super Tank is to limit the number of ports while also providing enough ports for functionality and possible process upgrades. TC ferrules input cold spots and hard to clean areas. The zero dead-leg flanges as discussed earlier are basically the same at the tank wall. When space is a concern, or the design is to optimize the vessel with fewer ports, equipment has been developed that allows for multiple process functions with one port.

The multifunction dip tube is one such device and has a couple of standard configurations; two function and three function. The two-function model combines the function of a dip tube, and CIP device into one port. The three-function device also incorporates a custom sparger. The dip tube can be engineered for a wide range of vessel sizes and requirements and like traditional spray devices can be custom drilled and indexed. Changes in the position of the actuator on the valve changes the function of the device (**Figure 8**).

Conclusions

While focused on process simulation testing for aseptic final filling and not necessarily process vessels intended for aseptic operations, the PDA had this to say about risk, “the risk analysis approach utilized must be compatible with the recognition that there is no acceptable level of risk associated with sterile products, regardless of the method of manufacturing. The goal is, and must always be, perfection in all elements of sterile product manufacture even where they are made using an aseptic process.”[4]

With this thought in mind and a focus on vessel design and construction, it is evident that not merely reducing but eliminating dead legs in vessels, and for that matter in all process piping should be the goal because of the significant long term positive benefits. The incremental upgrade cost associated with eliminating dead legs, when factored over the service life of the vessel is negligible. However, by implementing the Super Tank quality by design approach, the vessel is forever cleanable. Non-sterility, cross contamination as well as reduced validation efforts are risks that while they cannot be eliminated, they can be significantly reduced. The result is reduction in down time and cost savings over the life of the vessel.

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